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IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In the Application of)
STEPHEN P. COBBOLD *et al*)
Serial No. 08/289,532)
Filed 12th August 1994)
For: MONOCLONAL ANTIBODIES)
FOR INDUCING TOLERANCE)

Examiner: Gambel

Group Art Unit: 1806

DECLARATION

I, James Scott Crowe of The Wellcome Research Laboratories, Langley Court, South Eden Park Road, Beckenham, Kent, BR3 3BS, do hereby solemnly and sincerely declare as follows:

1. INTRODUCTION

1.1 I obtained the degree of B.Sc. (Hons) in Immunology from the University of Glasgow in 1980 and the degree of Ph.D. from the same university in 1983 for research into the antigenic variation in cyclically transmitted African trypanosomes. I have been employed by The Wellcome Foundation Limited since October 1983 working on various projects in the field of molecular and cell biology and since 1988 my work has been concerned with the therapeutic use of antibodies. I was appointed to the position of Senior Research Scientist in the Department of Cell Biology of The Wellcome Foundation in 1990 and I am currently head of the antibody engineering group within that department. The main focus of research within my group is the application of monoclonal antibodies for human therapy. I have been programme leader for eleven monoclonal antibodies through the research phase and a number of these antibodies are now undergoing clinical evaluation, including a humanised anti-CD4 monoclonal antibody.

1.2 I am familiar with the contents of United States Patent Application Serial No. 08/289,532 including the reasons given by Examiner Gambel for rejecting the claims in the office action mailed 14th February 1995 (Paper No. 23). This application is a continuation of United States Patent Application Serial No. 08/181,170 and I had the opportunity to discuss the patent application with Examiner Gambel at an interview on 3rd August 1994.

2. AMENDED CLAIMS

2.1 The outstanding office action is based on the claims 18 to 32 filed 12th October 1993 in the preceding application Serial No. 08/047,344. I understand that amended claims are to be filed in response to the outstanding office action in application Serial No. 08/289,532 and I am familiar with these amended claims. A number of changes are being made to the claims to obviate objections and expedite prosecution of the application and these are discussed below.

2.2 Method Claims: Claim 18 which relates to a method of treating a mammal in which it is desired to induce a state of immunological tolerance has been amended to state that the method consists essentially of the administration of the antibodies as defined in the claim. This clearly distinguishes the claimed subject matter from the disclosure of Qin *et al* which is discussed further below. Method claims 20 and 21 have been cancelled. Claim 30 has been amended to limit the antigens to transplantation antigens and immunoglobulins and a new method claim 34 has been added limited to the antigen being an autoantigen. Both claims 30 and 34 are limited to the use of the whole antibody to distinguish the claimed subject matter from Carteron *et al* which uses $F(ab')_2$ fragments. Method claims 31 to 32 have been deleted and a new method claim 33 has been added relating to the use of both a non-depleting anti-CD4 antibody and a non-depleting anti-CD8 antibody and one or more immunosuppressive therapies.

2.3 Kit claims: All claims to kits (previous claims 22 to 25) have now been cancelled.

3. Qin *et al* J. EXP. MED.

3.1 The main reference used by the Examiner as the basis for his prior art rejections is Qin *et al*, J. Exp. Med. 169, 779-794 (1989) and this reference was discussed with the Examiner at the interview in August 1994. The object of the work described by Qin *et al* was to establish "classical transplantation tolerance" in adult mammals and the word "classical" refers to the work of Medewar in the 1950's who obtained tolerance in new born mice by injection of bone marrow. Qin *et al* hoped to obtain the same type of tolerance in adult animals and the idea was to prime the recipient with donor bone marrow which expressed donor antigens which donor antigens thereby became autoantigens for the recipient. The immune system of the recipient had to be suppressed

to accept the bone marrow and the bone marrow then proliferated expressing the majority of the antigens in the tissue to be transplanted. As the immune system of the recipient became repopulated, the lymphocytes were educated to regard the antigens on the transplanted tissue as self. The result is that the lymphocytes are chimeric as between the donor and the recipient and the phenomenon is thus referred to as hemopoietic chimerism.

3.2 In this situation, immunological tolerance is induced by the bone marrow transplant and the problem is to get the bone marrow transplant established without it being rejected. Previously this had been attempted by methods including whole body irradiation (see Qin *et al*, page 779) and the requirement was to achieve sufficient immunosuppression so that hemopoietic chimerism could be established by the immune system being exposed to donor antigen whilst it was maturing (as in Medewar's experiments with new born mice) Once hemopoietic chimerism had been established, the donor graft should then be accepted.

3.3 Qin *et al* used antibody therapy as a means of immunosuppression to get the bone marrow transplant established. The authors said:

> *"We demonstrate here that transplantation tolerance can, in a number of strain combinations, be induced in the adult mouse by combining BM transplantation (BMT) together with parenteral administration of CD4 and CD8 mABs. "* (page 779)

It is quite clear that the authors considered hemopoietic chimerism resulting from the bone marrow transplantation as an essential (although not necessarily a sufficient) condition for the development of tolerance. In this connection, reference can be made to the "Discussion" section of the paper and, for example, statements such as the following:

> *"The development of chimerism and tolerance was dependent on the prevention of alloreactivity in both the donor and recipient T cell populations. "* (passage bridging pages 790 and 791)

> *"We can categorise the circumstances in which the BM + mAB protocol failed to achieve tolerance into two groups; those where chimerism was established and those*

where it was not. Those lacking chimerism we consider as examples of residual resistance/rejection.... Those situations where chimerism is insufficient to guarantee tolerance to skin grafts may present instances where a tissue (skin) - specific antigen is simply insufficiently represented in the small percentage of chimeric donor hemopoietic cells." (page 792)

3.4 The authors used non-depleting as well as depleting anti-CD4 and anti-CD8 antibodies in their attempts to get the bone marrow transplant established so that Qin *et al* is relevant to the present invention only accidentally. Although the authors were attempting to induce tolerance by a protocol which involved administration of a combination of anti-CD4 and anti-CD8 monoclonal antibodies (and in some cases these antibodies were non-depleting), there was no expectation that the antibodies themselves would induce tolerance and there is no suggestion that the antibodies did induce tolerance.

3.5 At page 782 to 784, the authors describe use of a protocol involving a cocktail of anti-CD4 and anti-CD8 antibodies together with bone marrow transplantation. The antibodies are all depleting IgG_{2b} antibodies so that this description is not relevant to the present invention.

3.6 At pages 784 to 785, the authors tested whether depletion was essential to enable the bone marrow transplant to become established by using $F(ab')_2$ fragments which lack the part of the antibody required for depletion. They found that a combination of a depleting anti-CD4 antibody and $F(ab')_2$ fragments of a depleting anti-CD8 antibody produced prolonged survival of skin grafts. The reverse protocol ($F(ab')_2$ fragments of depleting anti-CD4 antibody plus whole depleting anti-CD8 antibody) did not prolong survival of skin grafts and nor did either fragment or complete antibody alone (Table III, page 784). However, it should be emphasised once more that in all cases the survival of the skin grafts was related to the ability of the antibodies to allow bone marrow transplants to become established so that these transplants could then establish tolerance. None of the antibodies were used in an attempt to establish tolerance without bone marrow transplantation.

3.7 The authors go on to say:

An alternative way of treating with CD4 and CD8 mAbs without incurring cell depletion is to use non-lytic rat IgG_{2a} mAbs (Qin, S., et al, manuscript in preparation). In Table IV it can be seen that injection of these antibodies resulted in antigenic modulation but not depletion of the relevant subsets. As with the $rIgG_{2b}$ fragments, the $rIgG_{2a}$ CD8 mAb could contribute to tolerance if combined with a $rIgG_{2a}$ CD4 mAb. Remarkably, the $rIgG_{2a}$ CD4 mAb could also enable tolerance if combined with a $rIgG_{2b}$ CD8 mAb. However, the combination of r IgG_{2a} CD4 and CD8 mAbs was surprisingly ineffective." (page 785)

Again it must be emphasised that the passage quoted above is referring to the ability of the antibodies to allow bone marrow transplants to become established so that the bone marrow transplant could then induce tolerance. The antibodies are not used without bone marrow transplantation and there is no suggestion that the antibodies alone could induce tolerance.

3.8 In order to ensure that the method claims of the present application are clearly distinguished from the disclosure of Qin *et al*, these claims now state that the method of tolerance induction "consists essentially of" the antibody treatment. This clearly excludes the experiments of Qin *et al* where antibodies were administered for a different reason whilst tolerance was being induced by bone marrow transplantation. It should be mentioned that the present application includes a description of experiments in which bone marrow transplantation was used in combination with an antibody treatment. The results of these experiments are reported in Figures 7 and 8 and Tables 3 and 4. This work is not within the scope of the claims of the present application and is not intended to be part of the invention.

4 CARTERON *ET AL* J. IMMUNOL.

4.1 The Examiner has also cited Carteron *et al*, J. Immunol., 140, 713-716 (1988) and states that this paper teaches that the ability of CD4-specific antibodies to induce tolerance is independent of its ability to deplete $CD4^+$ cells. Although the Examiner has taken these words from the Carteron *et al* paper, in order to put them into perspective, it is necessary to look more closely at what the reference actually discloses in terms of experimental work. In fact, the reference is not concerned with whole antibodies at all but with the effect of $F(ab')_2$ fragments on tolerance

induction. In the passage from which the words used by the Examiner appear to be taken, the authors actually say:

> *"In the present study, we tested the hypothesis that F(ab')$_2$ anti-L3T4 could also permit the induction of immune tolerance. We used a rat IgG$_{2a}$ mAb against chicken ovalbumin (2C7) as an immunogen. In this study, we demonstrate that treatment of mice with F(ab')$_2$ anti-L3T4 at the time of first exposure to 2C7, like treatment with intact anti-L3T4, permits the induction of long lasting Ag-specific immune tolerance. This finding indicates that the ability of anti-L3T4 to induce immune tolerance is independent of its ability to deplete L3T4$^+$ cells".* (page 713)

4.2 It is to be assumed that the intact antibody would have been depleting but as already noted F(ab')$_2$ fragments lack the part of the whole antibody which is required to deplete the target cells. Accordingly, the authors had found an entity (F(ab')$_2$ fragments of the anti-L3T4 antibody) which could apparently induce tolerance to an antigen without depleting L3T4$^+$ cells and I think that this is all that the authors can have intended by the statement referred to by the Examiner. It is certainly not possible to conclude from the work of Carteron *et al* that depletion is irrelevant to the mechanism by which an intact depleting anti-L3T4 antibody can induce tolerance or that an intact non-depleting anti-L3T4 antibody would be capable of inducing tolerance.

4.3 The sites in the lymphoid architecture at which peripheral T-cell tolerance induction occurs are unknown and it is likely that a number of these sites lie deep within lymphoid follicles. It is known that antibody fragments such as F(ab')$_2$ fragments can penetrate solid tissues such as tumours to a greater extent than whole antibodies and it is conceivable that a F(ab')$_2$ fragment may gain access to regions of the lymphoid architecture inaccessible to a whole non-depleting antibody.

4.4 It has also been shown that cross-linking of the Fc region of a non-depleting anti-CD4 monoclonal antibody by Fc receptor positive cells is required to induce down modulation of the CD4 antigen on resting CD4 positive cells. This down modulation does not occur with a F(ab')$_2$ fragment, indicating that the mechanism of action of the F(ab')$_2$ fragment is likely to be different.

4.5 The mechanism by which tolerance was induced by whole depleting anti-CD4 antibodies

was not known at the date to which the present application is entitled but was assumed to involve depletion of $CD4^+$ T-cells. The mechanism by which $F(ab')_2$ fragments might induce tolerance was certainly not known and there was no means of knowing whether it was the same as for intact depleting anti-CD4 antibodies. Given the assumption that the latter mechanism involved depletion of $CD4^+$ cells, there was at least a possibility that the mechanisms were quite different. Furthermore, the mechanism by which depleting anti-CD4 antibodies depleted $CD4^+$ T-cells was not known although it was known to involve the Fc portion which is missing in $F(ab')_2$ fragments. It was quite unpredictable whether a non-depleting anti-CD4 antibody with the whole Fc portion intact would be capable of inducing tolerance without depletion. The fact that induction of tolerance has been reported without cellular depletion against a small number of antigens by $F(ab')_2$ fragments of an anti-CD4 (or L3T4) antibody used at large doses does not suggest that use of an intact non-depleting anti-CD4 antibody used at appropriate doses without cellular depletion would also induce tolerance.

4.6 As I understand the office action mailed 14th February 1995, the Examiner is seeking to combine the teaching of Carteron *et al* with the teaching of Qin *et al*. I cannot see how such a combination can lead to the present invention since, as I have already explained, Qin *et al* do not use antibodies to induce tolerance but rather to produce a sufficient degree of immunosuppression for bone marrow transplants to become established.

5. WALDMANN, ANN. REV. IMMUNOL.

5.1 The article by Waldmann cited by the Examiner (Ann. Rev. Immunol., 7 407-44 (1989) has the classic review format in that the intention of the author is to alert the reader to papers which have been published relevant to the subject in question. It is not to be expected that mention of a paper in a review article of this sort will disclose any more than the paper itself discloses and usually the review will disclose very much less. The person skilled in the art reading the review would be expected to consult the original paper in the case of any work which interested him.

5.2 The most relevant section of the Waldmann review is headed "Monoclonal Antibodies for the Induction of Tolerance" and is at pages 425 to 430 and particularly pages 425 to 428. Many of the papers mentioned in the review have already been cited in their own right in the prosecution

of the present application. I will comment briefly on all of the papers referred to in the particularly relevant part of the review at pages 425 to 428 identified by the number used by Waldmann himself. However, I should mention that the first reference in this part of the review to Benjamin and Waldmann "(123,124)" should probably read "(122,123)" since "124" is the paper by Gutstein *et al* mentioned immediately afterwards.

5.3 Reference 122 is Benjamin & Waldmann, Nature, 320, 449 (1986). The work disclosed is this paper relates only to depleting anti-CD4 antibodies.

5.4 Reference 123 is Benjamin *et al*, J. Exp. Med., 163, 1539 (1986). The work disclosed in this paper was concerned mainly with the antiglobulin response and involved use of a depleting (IgG_{2b}) anti-CD4 antibody.

5.5 Reference 124 is Gutstein *et al*, J. Immunol., 137, 1127 (1986). The list of references in the Waldmann review quotes the page as "1121" but it is clear that "1127" is intended. It can be seen from Table I of Gutstein *et al* that the anti-L3T4 antibodies used in the study were IgG_{2b}, i.e. depleting, antibodies. The reference to an IgG_{2a} antibody in the table is to an anti-OVA antibody used as antigen.

5.6 Reference 126 is Benjamin *et al*, Eur. J. Immunol., 18, 1079 (1988). This paper is largely concerned with mechanisms of tolerance induction and used the anti-CD4 antibody YTS 191.1 which is a depleting IgG_{2b}. However, the authors also worked with $F(ab')_2$ fragments (which would not deplete the population of target cells) and with reference to these fragments they say:

> *"We show here that (a) $F(ab')_2$ fragments of a CD4 mAb can also provide the tolerogenic milieu without cellular depletion."* (page 1079 right hand column)

> *"YTS 191.1 $F(ab')_2$ fragments were produced and shown to be active and free of contaminating intact mAb... Depletion of Th cells is therefore not a necessity for either immunosuppression or tolerance induction to HGG."* (page 1081, right hand column to page 1082 right hand column under the heading "Depletion of Th cells is not necessary for CD4 - mediated tolerance induction".)

Accordingly, the same comments apply to this paper as to Carteron *et al* discussed in section 4 above. It was quite unpredictable based on this disclosure of Benjamin *et al* whether a non-depleting anti-CD4 antibody with the whole Fc portion intact would be capable of inducing tolerance without depletion.

5.7 Reference 127 is Goronzy *et al*, J. Exp. Med., 164 911 (1986). In the work reported in this paper the authors used a depleting anti-L3T4 antibody (IgG_{2b} - see page 912) and the authors do not claim to have achieved tolerance but rather refer to "long term unresponsiveness" (page 922).

5.8 Reference 45 is Qin *et al*, Eur. J. Immunol, 17, 1159-1165 (1987) and is, of course, a different paper from the Qin *et al* reference discussed above in section 3. The list of references in the Waldmann review quotes the page number as "1559" but it is clear that "1159" is intended. The work described in this paper followed the discovery that a depleting anti-CD4 monoclonal antibody could induce tolerance and the authors investigated the use of a pair of depleting (IgG_{2b}) anti-CD4 antibodies which recognised different epitopes of the CD4 antigen. The authors say:

> *"The antibody pair is shown to exhibit clear synergistic lysis in vitro and demonstrates improved immunosuppressive and lytic potency in vivo"* (page 1159, right hand column)

> *"In this report we have shown that a pair of mAbs (both rat IgG_{2b}), to non-overlapping epitopes of the mouse CD4 molecule, have a greater immunosuppressive potency than either one use alone."* (page 1164, left hand column)

> *"In the model of HGG tolerance, as little as 60 ng of the mAb pair was able to allow tolerance compared to 600 ng of either YTS 191.1 or YTA 3.1 alone."* (page 1164, right hand column)

Thus, although the two anti-CD4 antibodies used in this work were depleting, the authors found what appeared to be a synergistic effect so that tolerance to the antigen HGG was induced using a dose of the antibody combination which was below that which would be expected to be necessary

to bring about significant depletion of the relevant population of T-cells. The nature of this synergistic effect remains unexplained and it is by no means clear whether or not tolerance induction by this combination of depleting antibodies involved some degree of depletion. The paper does not disclose or suggest in any way that a non-depleting anti-CD4 antibody would be able to induce tolerance to an antigen.

5.9 Reference 128 is Gutstein & Wofsy, J. Immunol. 137, 3414 (1986). In this paper the authors looked at the effect of $F(ab')_2$ fragments of an anti-L3T4 antibody on the response of mice to the antigen BSA. The intact antibody can be assumed to be depleting but, as already noted, $F(ab')_2$ fragments lack that part of the antibody required to deplete the population of target cells. The authors concluded that:

> *"In the present study, we used $F(ab')_2$ fragments of anti-L3T4 to prove that the ability of anti-L3T4 mAb to inhibit humoral immunity is not dependant on depletion of $L3T4^+$ cells."* (page 3417, left hand column)

Again, as with the Carteron *et al* reference discussed above in Section 4, all that this means is that the authors had found an entity ($F(ab')_2$ fragments) that produced the effect discussed (in this case immunosuppression rather than tolerance) without depletion of $L3T4^+$ cells. It is not possible to draw conclusions from this result about the likely effect of an intact non-depleting antibody.

5.10 Reference 129 is the Carteron *et al* reference discussed above in section 4.

5.11 Reference 130 is a paper by Coulie *et al*, Eur. J. Immunol. 15, 638-640 (1985) in which the authors reported that in the mouse a single injection of an antibody specific for the murine L3T4 antigen "completely abolished both primary and secondary T-dependent antibody responses" (page 638). Reference 131 is a review article by Charlton *et al*, Immunol. Today, 9, 165 (1988) and the authors conclude in the final paragraph that:

> *"The available collected data show that depletion of $L3T4^+$ cells in vivo is not necessary to abrogate $L3T4^+$ cell function, and that blockade of the L3T4 antigen without depleting cells abrogates the response to soluble antigen, to allografts and*

to autoantigens." (page 166).

Whilst Coulie *et al* and Charlton *et al* may suggest that a non-depleting anti-CD4 antibody may block $CD4^+$ T-cell function and thus exert an immunosuppressive effect, there is no suggestion that non-depleting anti-CD4 monoclonal antibodies would be capable of inducing immunological tolerance to an antigen.

5.12 References 75 and 132 mentioned on page 427 of the Waldmann review article are puzzling since both are identified in the same way as "Qin *et al*, (1988) (Submitted)" and I cannot identify the paper(s) concerned with complete certainty. From the titles quoted which are as follows:

75 - "Induction of classical transplantation tolerance in the adult. Bone marrow transplantation to secure tolerance in the adult."; and

132 - "Classical transplantation tolerance in the adult";

I believe that references 75 and 132 are probably both intended to be the Qin *et al* paper in J. Exp. Med., 169, 779 (1989) which is discussed in section 3 above. This Qin *et al* paper is not included in the list of references in the Waldmann review with a full citation to the paper as published and the title of the published paper was:

"Induction of classical transplantation tolerance in the adult".

5.13 Mention should also be made of the passage of page 426 of the Waldmann review which reads:

> *".... and recently S. Qin, H. Waldmann, S. P. Cobbold and Y. N. Kong (unpublished) have shown that a rIgG_{2a} CD4 mAb may also permit tolerance without cell depletion."*

This passage does not say that it refers to any specific publication and, on the contrary, the work is stated to be unpublished. In fact, it seems likely that the passage is referring to some at least

of the work included in the present application. Cobbold and Waldmann are inventors of the present application and Waldmann is, of course, the author of the review article. Qin and Kong also participated in the work on which the present application is based but as explained by Professor Waldmann in his declaration dated 22nd September 1993, their contributions were not inventive. As far as the passage itself is concerned the suggestion that "a $rIgG_{2a}$ CD4 mAb may also permit tolerance without cell-depletion" is unsupported by any experimental results and is not enabling.

5.14 The paragraph from two lines below figure 7 on page 427 to two lines below figure 8 on page 428 all relates to the use of bone marrow transplantation to establish hemopoietic chimerism. This has already been discussed above in section 3 in the context of the Qin *et al* J. Exp. Med. paper and as I have already noted reference 132 appears to be a reference to the same paper. Reference 133 is the original paper from Medewar in the 1950s which established the concept of producing transplantation tolerance in new born mice by bone marrow transplantation. The only other reference in the section of the Waldmann review from pages 425 to 428 is to "Benjamin *et al* (manuscript in preparation)". It is not clear what publication (if any) this became but the mention of hemopoietic chimerism shows that the work clearly related to the use of bone marrow transplantation to establish tolerance.

5.15. In discussing the Waldmann review (page 12 of the office action mailed 14 February 1995 the Examiner states:

> *"Waldmann teaches the importance of CD4 therapy in autoimmunity including the use of non-depleting F(ab')$_2$ fragments of CD4 monoclonal antibodies."* (pages 423-425).

It should be noted that the section of the Waldmann review referred to by the Examiner (pages 423-425) is not in the part which is concerned with tolerance, but is in the part headed "Immunosuppression" (general heading page 408). It is self evident that immunosuppression may have the potential to alleviate some symptoms of autoimmune conditions although this may be at some cost to the patient in terms of a generally reduced ability of the immune system to fulfil its normal function. There is no suggestion at pages 423-425 of the Waldmann review that a non-

depleting anti-CD4 monoclonal antibody can induce tolerance to an autoantigen.

5.16 The Examiner goes on to say:

> *"Waldmann further teaches that it was known in the art that the improved therapeutic effect of short-term therapy with both CD4- and CD8- specific antibodies compared to CD4 antibody alone in diabetes that develops following low dose steptozotocin (sic) or experimental thyroiditis (page 424, line 30-36) as reported by Kantwerk et al (Clin. Exp. Immunol. 70:585, 1987) and Kong et al (Immunobiology (Suppl.) 3:30, 1987)".*

The reference on page 424 of the Waldmann review shows that again the papers by Kantwerk *et al* and Kong *et al* are discussed in the section of the review relating to immunosuppression. Both publications are concerned with investigating the role of different T-lymphocyte subsets in models of autoimmune disease and the object of administering different antibodies (anti-L3T4, anti-Lyt-2) was to deplete the population of target T-cells so that the effect could be observed. There is no suggestion in either publication of the use of non-depleting antibodies and there is no suggestion of tolerance induction.

6 WALDMANN, AM. J. KID. DIS.

6.1 The Examiner has also cited a paper by Waldmann in American Journal of Kidney Disease, XI (2), 154-158 (1988) and states that this teaches that anti-CD4 antibodies can induce tolerance without cell ablation and that anti-CD4 and anti-CD8 antibodies in conjunction with bone marrow cells can lead to tolerance. This paper does not disclose new experimental work but is again a review article. As stated by the author in the second paragraph:

> *"In this report I will briefly review some of our published work directed to these themes and will offer views on potential future applications".*

6.2 The Examiner refers first to tolerance induction without cell ablation as mentioned on page 156 and presumably has in mind the discussion of reference 13 (Qin *et al*, Eur. J. Immunol., 17

1159-1165 (1987) and the subsequent reference to "Benjamin and Waldmann, unpublished results" which clearly became the paper in Eur. J. Immunol., 18, 1079 (1988). The review article does not add anything to these published papers both of which have already been discussed above in paragraphs 5.8 and 5.6 respectively. The mention of tolerance induction by anti-CD4 and anti-CD8 antibodies together with bone marrow transplantation presumably refers to the discussion of reference 5 which is identified as "Qin S, Cobbold S P, Waldmann H: Induction of classical transplantation tolerance in the adult (submitted)". This is clearly a reference to the paper in J. Exp. Med., 164, 779-794 (1989) discussed above in section 3 and the reference to this paper in the review article again adds nothing to the disclosures of the paper itself.

7. ENABLEMENT

7.1 Section 19 of the outstanding office action relates to enablement and I think that the nub of the Examiner's objection is to be found in the penultimate paragraph on page 3 where the Examiner says:

> *"Therefore, is does not appear that the asserted operability of the claimed method and compositions for inducing tolerance in humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone".*

As I understand it, the Examiner starts from the proposition that experience with antibody therapy generally to date suggests that this type of therapy is not effective in humans. He then adds the proposition that data in the mouse is not reasonably predictive with regard to humans. He also considers that there is insufficient data to enable the invention over the range claimed with respect to antigen. I will comment on these propositions and also on the references listed by the Examiner in support of his position.

7.2 With regard to antibody therapy generally, it is correct to say that this has been the subject of unrealistic expectations and these unrealistic expectations have not, of course, been fulfilled. For example in the treatment of cancer it was never likely that antibodies would be able to

penetrate and destroy large solid tumours. This does not mean that antibody therapy generally is ineffective and the amount of time and money that the pharmaceutical industry world wide is investing in the development of therapeutic antibodies shows that the industry is confident that many antibodies will prove effective as therapeutic agents. I attach marked exhibit "JSC1" a copy of a table headed "Status of New and Existing Monoclonal Antibodies" which is taken from a publication from 1994 "Plan A - Innovations in Anti-Cancer Drugs II 1993-2000", Volume II. This is a marketing report produced by Plan A, Box 3013, Stanford, Carolina 94309 and the relevant section is an update on antibodies currently undergoing evaluation as potential therapeutic agents. The table extends over 7 pages and has over 150 entries which is a reflection of the fact that far from not being considered useful for therapy in humans, monoclonal antibodies are currently the subject of a very considerable amount of interest and work. Many of the antibodies are still at the stage of pre-clinical evaluation but over 50 of the entries refer to Phase I or Phase II Clinical Trials.

7.3 I referred above to the treatment of cancer as a field in which antibodies had been the subject of unrealistic expectations. However, this does not mean that antibodies have no place in cancer therapy, only that they should be used in an appropriate way. My own company is developing a mouse monoclonal antibody (PANOREX) for the treatment of colorectal cancer in an adjuvant setting and the results of a successful Phase III clinical trial were published in Reithmüller *et al*, The Lancet, 343, 1177-1183 (1994). PANOREX received marketing approval in Germany earlier this year and further Phase III clinical trials are ongoing world wide.

7.4 The Examiner continues to place great reliance on the article by Harris and Emery, TIBTECH, 11, 42-44 (1993) and in particular the statement in this article that:

> *"There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy."*

In referring to argument filed in response to a previous office action the Examiner says:

> *"Applicant did not agree with the Harris et al reference because of the bias of the meeting to promote various commercial organisations involved in the engineering*

of antibodies including Harris himself, who works for Scotgen".

I do not believe that this was ever Applicant's position and it is certainly not my position. I disagree with the statement by Harris and Emery because I know from my own experience in the development of therapeutic antibodies that it is wrong and can be demonstrated to be wrong. The comment about the nature of the meeting and the background of Harris was simply an aside going some way towards explaining why such a statement may have appeared in print under his name. The statement that "there is little future for the use of rodent mAbs for in vivo human therapy" is inconsistent with the recent marketing approval for PANOREX (a mouse antibody) and the fact that many of the antibodies currently in development are rodent antibodies. The antibodies listed in exhibit JSC 1 include rodent antibodies, chimeric antibodies and humanised antibodies and my opinion, which I believe is generally shared by those involved in the development of therapeutic antibodies, is that all three types of antibody have a place as therapeutic agents in humans.

7.5 In view of the fact that the Examiner is adopting the position that adverse reactions to antibodies represent a major limitation to antibody therapy, it may be helpful to discuss the nature of these reactions in more detail. Two possible adverse reactions are xenosensitisation and an anti-idiotype response and it is important that these should not be confused. Xenosensitisation results from the reaction of the immune system of one species against an antibody from another species which is seen as a foreign protein. In the case of a mouse antibody used in man this is the so-called "HAMA" response and the possibility of such a reaction must always be borne in mind when using a rodent antibody for therapy in man. However, the possibility of such a reaction has not been sufficient to deter many companies from developing rodent antibodies and this includes the development of PANOREX by my own company.

7.6 The anti-idiotype reaction arises against the three dimensional structure of the surface of the antigen binding region of an antibody which may be recognised as foreign by the host. All antibodies have an idiotype so that there is the possibility of an anti-idiotype reaction against any antibody whether it be rodent, chimeric or humanised and indeed the likelihood of an anti-idiotype reaction is no different as between these three types of antibody. An anti-idiotype reaction is potentially important since it can block the antigen binding site of the antibody. A serious anti-idiotype response precludes further therapy and has the potential to render any antibody unusable

therapeutically. I use the words "has the potential" because in practice the anti-idiotype response does not, in general, render antibody therapy unusable. It is something that must be (and is) monitored in any antibody therapy and the extent to which it occurs seems to depend on the disease from which the patient is suffering as well as the specific monoclonal antibody. Thus with the humanised anti-CDw52 antibody CAMPATH-IH in the treatment of non-Hodgkin's lymphoma, only 3 out of 70 patients developed an anti-idiotype response. On the other hand in use of the same antibody in the treatment of rheumatoid arthritis 50% or more of patients developed an anti-idiotype response and it may be that rheumatoid arthritis patients are more susceptible for some reason to developing such an immunogenic response. However, even in this case, the fact that a relatively high proportion of the patients develop an anti-idiotype response to CAMPATH-IH is not seen as precluding the use of the antibody in the treatment of rheumatoid arthritis.

7.7 It is generally possible to live with the responses discussed above in the development of antibody therapy in the sense that they can be controlled if they arise and therapy continued. However, if a response becomes a particular problem in any given therapeutic application, then an engineered variant of the antibody can be developed to reduce the problem and this is essentially the position as set out by Jolliffe in the article in Intern. Rev. Immunol. 10, 241-250 (1993) referred to by the Examiner. The mouse antibody OKT3 had proven effectiveness in the therapy of renal allograft rejection but a problem arose in some cases with cytokine release syndrome which resulted in severe first dose side effects. Cytokine release syndrome is not well understood but is known to be related to binding of the antibody to Fc receptors so that, as reported by Jolliffe, OKT3 was engineered to re-construct the Fc region and at the same time the opportunity was also taken to humanise the antibody. This is simply an illustration of the point mentioned above that rodent, chimeric and humanised antibodies all have a place in therapy. An extreme form of the reactions discussed above is anaphylactic shock but this is a known event which can be readily reversed if it occurs, for example by use of adrenaline.

7.8 The Examiner also refers to the statement at page 42, right hand column of Harris and Emery about the anti-idiotype response and what they actually say is that generally the HAMA response is greatly reduced for chimeric antibodies,

"However, the residual HAMA response to chimeric antibodies is mainly anti-

idiotypic, therefore repeated dosing is ineffective."

This statement is a little confused in the sense that as I have already explained the HAMA response is a result of xenosensitisation and should be distinguished from the anti-idiotype response. Chimeric antibodies have an intact rodent variable region so that there is still the potential for a HAMA response to occur. My understanding of what Harris and Emery are saying is that this HAMA response is greatly reduced and that any response that remains is likely to be an anti-idiotype response. If this arises in a serious way then repeated dosing will be ineffective. If this is what Harris and Emery are saying, then I do not disagree. They clearly do not think that the anti-idiotype response, which can arise equally with humanised antibodies, is sufficient of a problem to render antibody therapy unusable.

7.9 The Examiner then refers to Bach *et al*, Immunol. Today, 14, 421-425 (1993) which he characterises as a

"recent review of the safety and efficacy of therapeutic monoclonal antibodies in clinical therapy"

which he says reasserted problems associated with antibody therapy "with a particular emphasis on xenosensitisation". The Examiner appears not to have appreciated the nature of this article and, in fact, I can speak about it from personal experience. The article is a report of a meeting organised by the European Economic Community and held in Paris in December 1992. The participants are listed on page 425 and included both the inventors of the present application (Herman Waldemann and Stephen Cobbold) and myself. The meeting was not intended to be a balanced scientific assessment of the relative merits of different types of antibody but focused largely on how academic groups could conduct clinical work on antibodies. It was recognised that many academic institutions did not have the technology or the resources to produce chimeric or humanised antibodies and it was agreed that mouse antibodies could be used for initial testing. This conclusion is quite inconsistent with the negative view of mouse antibodies put forward by the Examiner and as a participant in the meeting I can say that it is simply not correct that the meeting reasserted problems associated with antibody therapy. It is correct to say that the meeting recognised that the pharmaceutical industry preferred chimeric or humanised antibodies over rodent

antibodies but the reasons for this preference are by no means related only to the potential of each different type of antibody to cause adverse reactions when administered to humans. A major reason why pharmaceutical companies prefer chimeric and humanised antibodies is because they are invariably recombinant proteins which means that there is much greater control over their production and purification which means, in turn, that obtaining regulatory approval will be easier.

7.10 The Examiner also refers to Russell *et al*, Bri. Med. J., 305, 1424-1429 (1993) although it is not entirely clear which parts of this article he has in mind since "305" is the volume number and not a page number as suggested. The Examiner may be referring to page 1426 and the passage which starts:

> *"Monoclonal antibodies offer a realistic alternative to these immunosuppressive drugs, and this is perhaps their most useful current application ... In common with other immunosuppressive antilymphocyte monoclonal antibodies it [OKT3] does not stimulate a strong antimouse response... Many other immunosuppressive monoclonal antibodies have been shown to have activity in humans. Among the most promising are antibodies against the lymphocyte antigens CD4, Tac and CDwS2 (see below), all of which have been humanised by CDR-grafting."*

The Examiner may also be referring particularly to the final complete sentence in the left hand column on page 1426 which says:

> *"Monoclonal antibodies against CD4 inhibit the function of helper T-cells and have been used with varying success to treat acute rejection of renal allografts, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, relapsing polychondritis, systemic vasculitis, and mycosis fungoides."*

This is hardly a catalogue of failure and if a similar statement could be made about a chemical pharmaceutical the record would be considered as very good indeed. However the point needs to be made that Russell *et al* are talking about the therapeutic use of antibodies as immunosuppressive agents. Immunosuppression may have serious consequences for the patient in terms of leaving him more susceptible to adventitious infections so that dosing in any trial, and particularly initial trials,

would be conservative. It may well be that some of the less than satisfactory results could be attributed to the dosing being two cautious.

7.11 The Examiner also refers to Nossal which is a whole chapter (pages 571-586) from the textbook "Fundamental Immunology" 2nd Edition (1989). In particular, the Examiner refers to a statement by Nossal about the use of an anti-CD4 antibody in the case of a pancreatic islet allograft. What Nossal says is:

> *"A single injection of anti-CD4 antibodies produces profound but transient immunosuppression. If, during this transient phase, a protein antigen is injected, a state of specific unresponsiveness to later immunogenic challenge with the same protein is noted. Unfortunately it has not been possible to extend this idea to a transiently anti-CD4 treated mouse then given a fetal pancreatic islet allograft, where anti-CD4 prolongs graft survival but does not allow indefinite maintenance (K. Burkhardt and T. Mandel, unpublished results)"*

The problem with this statement is that it relates to unpublished results so that we do not know how the experiment was carried out. It is to be assumed that the antibody was depleting but we do not know how much antibody was administered or over what period of time. It is not surprising that a depleting antibody can be administered in a manner which failed to achieve tolerance and I cannot see that this has any relevance to the present invention.

7.12 Chen *et al* in Transplantation Proceedings, *26(4)*, 2433-1434 (1994) demonstrate that a combination of blocking anti-CD4 and anti-CD8 monoclonal antibodies was successful in inducing tolerance to all allografts attempted including fully mismatched mouse skin allografts. The only failure of tolerance induction using this blocking protocol was in grafting a xenogenic skin graft. This is an exceptionally difficult model for tolerance induction due to the extreme immune response generated against the graft and it is very unlikely that this magnitude of immune activation would occur elsewhere.

7.13 The study by Watson *et al* reported in Journal of Surgery, *80(11)*, 1389-1392 (1993) using a large animal model (dog) as a means of progressing the pre-clinical evaluation of anti-CD4 and

anti-CD8 monoclonal antibodies for tolerance induction has a major flaw. The CD4 antigen in the dog is present on neutrophils as well as on a sub-set of T-cells whereas this is not the case in mice or in man. This makes this model singularly inappropriate for a study of the role of an anti-CD4 monoclonal antibody for tolerance induction. The presence of the CD4 antigen on dog neutrophils suggests that in this species the mechanism of peripheral tolerance induction may involve a blockade of a number of other molecules important in T-cell activation such as CD3, CD28 and CD29. Therefore results obtained using anti-CD4 monoclonal antibodies in the dog are meaningless.

7.14 I have referred above to CAMPATH-1H which is an antibody that was for a time under development by Wellcome. For the sake of completeness, I should mention that Wellcome made a public announcement on 26th September 1994 that the company had ceased clinical development of CAMPATH-1H as they believed that the compound was not likely to have adequate commercial potential in those conditions of prime strategic importance to Wellcome. The decision for Wellcome to terminate development of CAMPATH-1H cannot affect the data which has already accumulated to demonstrate the therapeutic effectiveness of the antibody and has no impact on conclusions that I have drawn from data relating to the antibody.

8. TOLERANCE INDUCTION IN ANIMAL MODELS AND IN HUMANS

8.1 On page 5 of the outstanding office action, the Examiner refers to the experimental work on which the present application is based and makes the following comments:

> *"Although the applicant has exemplified some success with the instant methods and compositions for tolerance induction for certain antigens in certain mouse strain combinations with non-immunogenic rat antibodies, there is no positive evidence or nexus that such therapy would work in humans or would work for any antigen system. The standards of enablement and operability that are commensurate in scope with the instant invention would be the induction of tolerance for weak and strong antigenic barriers in human therapy. Therefore, applicant's arguments were not convincing in that the murine examples presented in the application would be predictive for the successful indication of tolerance to the scope of antigens in*

humans."

I take this passage to mean that the Examiner does not consider that the work reported in the specification is sufficiently predictive of the results that could be achieved in humans. I believe that the Examiner is wrong to take this view in that the mouse represents the best model available in the present circumstances and is a generally accepted starting point for immunological studies. In addition, and perhaps more important, there is now a considerable body of evidence in the scientific literature that the results in mice are predictive of the position in humans, this evidence being the successful use of anti-CD4 monoclonal antibodies in the treatment of autoimmune conditions in animal models and in humans.

8.2 The treatment of autoimmune conditions is one of the major areas where induction of tolerance is of advantage and a considerable number of reports have now appeared in the scientific literature relating to the use of anti-CD4 antibodies in animal models of autoimmune conditions. As pointed out in a review by Riethmüller *et al* entitled "Human-Murine Chimeric CD4 Monoclonal Antibodies: A Modern Panacea for Autoimmune Disease?" which was published in Immunology Series, Volume 59, Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, edited by J-F Bach:

> *"In the long list of established experimental autoimmune diseases in the mouse, there is virtually none that has not been treated with monoclonal CD4 antibodies ... None of various model systems turned out to be a therapeutic failure..."* (page 263)

In most cases, the object of the work was simply to observe the effect of the antibody in the model system in question. The fact that an effect was seen (as was invariably the case) does not of itself demonstrate the re-establishment of functional tolerance to the autoantigen which is the subject of the destructive immune response.

8.3 However there are some cases where the experimental work has effectively demonstrated that functional immune tolerance has been re-established. Shizuru *et al*, Science, 240, 659-662 (1988) investigated the effect of a depleting anti-CD4 monoclonal antibody in the non-obese diabetic (NOD) mouse model. This is a mouse that spontaneously develops diabetes resembling

human insulin-dependent diabetes mellitus (IDDM). As stated by the authors:

> *"We have been able to block the progression and subsequent expression of overt diabetes in NOD mice by a course of treatment with a monoclonal antibody to L3T4. Such an approach may be feasible for treatment of patients with subclinical manifestations of IDDM, since we show that antibody therapy initiated late in disease progression was effective in reversing islet cell destruction. Moreover, upon cessation of therapy the mice have remained disease-free without further treatment."* (page 659, centre column)

8.4 Hutching *et al* (Eur. J. Immunol., 22, 1913-1918 (1992)) used the same model but investigated the effect of a non-depleting anti-CD4 monoclonal antibody. The authors said:

> *"We show that a short course of non-depleting anti-CD4 monoclonal antibody YTS 177.1 (CD4 NDP Ab) is sufficient to provide NOD mice with long-lasting protection from the ß cell destruction transferred by diabetic donor spleen cells. Furthermore, responses to foreign antigens remain intact after cessation of antibody treatment."* (page 1913, right hand column

.....

> *"Our data suggests that tolerance to ß cell antigens can be established in mice already programmed to develop IDDM by administration of a CD4 NDP Ab."* (page 1917, left hand column)

.....

> *"The fact that T cells can be brought under tighter control even when actively engaged in an aggressive response, suggests that tolerance therapy with CD4 NDP Ab may offer a safe therapeutic approach to restrain autoimmune disorders with the minimum of disruptive intervention."* (page 1917, right hand column).

8.5 The use of anti-CD4 antibodies in the treatment of autoimmune conditions in man is now becoming well established. For example, a literature search for references to the therapeutic use

of CD4 antibodies in man provided well over 100 references describing work on the treatment of autoimmune conditions of one sort or another. The search was not able to distinguish between anti-CD4 antibodies which deplete CD4 T-cells and anti-CD4 antibodies which have a blocking rather than a depleting effect although both types of antibody are under investigation. Some of the references will be re-publication of essentially the same data in more than one place but the number of references found is still an impressive total. The sheer number of references involved makes it impossible to discuss each one individually, however, review articles give a good idea of the stage which the work has reached.

8.6 In the review by Riethmüller *et al* mentioned above in the context of animal models of autoimmune conditions, the authors go on to discuss the clinical data on the use of anti-CD4 monoclonal antibodies in autoimmune conditions in man and the results are summarised in Table 2 on page 267. I would conclude from this data that anti-CD4 antibodies have also had at least some effect in all autoimmune conditions in man in which they have been tried.

8.7 The following review in volume 59 of Immunology Series by Morel *et al* relates to "CD4 Antibody Therapy in Chronic Inflammatory Dermatological Diseases" (page 271-276). The authors say:

> "*The excellent clinical response of psoriasis to CD4 antibody therapy, together with the good tolerance observed in most patients who received the treatment, indicates that CD4 mAb may be a potential tool in the management of other severe dermatoses.*" (page 274)

before going on to review the use of anti-CD4 antibodies in these conditions.

8.8 In another review entitled "From Antilymphocyte Serum to Therapeutic Monoclonal Antibodies: First Experiences with a Chimeric CD4 Antibody in the Treatment of Autoimmune Disease" (Reithmüller *et al*, Immunological Reviews 1992, No. 129, pages 81-104) the authors discuss in turn the following conditions:

Rheumatoid arthritis

Chronic inflammatory bowel disease (Crohn's disease and colitis ulcerosa)

Psoriasis

Chronic autoimmune hepatitis

Polychondritis, uveitis posterior, mysathenia gravis and lupus erythematodes

and confirm the conclusion that anti-CD4 monoclonal antibodies have been effective in all autoimmune conditions in which they have been tried.

8.9 The dangers of profound immunosuppression in human patients are readily apparent and it is highly preferable to treat autoimmune disease by induction of tolerance rather than by immunosuppression. Although the animal data shows that tolerance can be induced in animals, none of the clinical data that I have referred to above yet provides scientific proof of the induction of tolerance in man. There are a number of reasons for this. First, the object of clinical trials in man is to evaluate safety and therapeutic effectiveness not to provide formal scientific proof of effects such as induction of tolerance to an autoantigen. It would be neither practical nor ethical to conduct in man experiments of the type that have established tolerance induction in animals. Second, the dangers of bringing about profound immunosuppression in man have led to the doses of anti-CD4 antibody which have been administered to man being very conservative. In addition, Phase I trials require a stepwise increase in the dose with monitoring of the effects to ensure safety. The consequences of immunosuppression may not be an acute phenomenon so that there has been a need to observe patients over a period at each dosage level to ensure that they do not succumb to infection. For this reason, dose escalation studies have of necessity been slow.

8.10 The doses which have been used up to now in man are considerably lower on a per kilogram basis (orders of magnitude lower) than those which have been used in animals to induce tolerance. In my opinion, in the treatment of autoimmune conditions in man, the work currently being undertaken involves the use of doses which are very much sub-optimal but yet good results are still being achieved. I find this very encouraging. I believe that increased doses of anti-CD4 antibody will induce functional immune tolerance to autoantigens in the treatment of autoimmune conditions. In the meantime, based on the results which have been obtained in animals and the results obtained so far in man, I believe that it is safe to predict that the induction of tolerance to autoantigens in the treatment of autoimmune conditions can be achieved in man by the administration of non-depleting anti-CD4 antibodies in accordance with the teaching of the present application.

9. ENABLEMENT OVER A RANGE OF ANTIGENS

9.1 In section 19B of the outstanding office action, the Examiner has questioned whether the data given in the present application, which is confined to certain specific antigens, has enabled the invention over the whole range of antigens claimed. It is well established that antigens differ in the response that they evoke from the immune system with some antigens evoking a much stronger response than others. The present application does not suggest that tolerance can be induced to all antigens in all circumstances using the same protocol and to do so would be over simplistic. What the present inventors have provided is the basis for arriving at a means for inducing tolerance to a range of antigens using a protocol adapted to the antigen in question. Some experimentation will be necessary in each particular case but I believe that the amount of experimentation involved will be reasonable in the circumstances.

9.2 The Examiner has specifically referred to papers by Charlton & Mandel, Immunol. Cell. Biol., 69, 109 (1989) and Carteron *et al*, J. Immunol., 140, 713-716 (1988). In both cases the work reported is outside the scope of the present invention and in terms of their effect on enablement, neither does more than illustrate the point that the tolerance induction protocol needs to be adapted to the antigen. Charlton & Mandel were apparently unable to induce tolerance to ovalbumin which is a protein cleared very quickly from the circulation so that it is quite likely that by the time that a tolerance permissive environment had been established (if it was) all antigen had been cleared.

10. CLARITY OF TERMINOLOGY

10.1 In section 21 of the outstanding office action, the Examiner has objected that the terminology in the claims is not sufficiently clear and he seems particularly concerned with the wording

> *"to induce an immunological tolerance permissive environment within said mammal in the presence of said antigen such as to induce the said state of immunological tolerance"*

I believe that this wording is clear in the context of the present invention.

10.2 One problem that the Examiner appears to have with this wording is the term "immunological tolerance" itself and he appears to be suggesting that Applicants use the terms "tolerance" and "immunosuppression" interchangeably. I have not been able to find the examples of this usage that the Examiner has in mind in his comments at page 8, end of second complete paragraph of the office action. There is a clear distinction in the mind of any immunologist between immunosuppression and tolerance in that immunosuppression involves a general down regulation of the immune system in reacting to any antigen which is recognised as non-self whereas tolerance is antigen specific and involves a failure to the immune system to react to one specific antigen which would otherwise be recognised as non-self whilst the immune system retains the ability to react to other non-self antigens. It is thus the antigen specific nature of tolerance which distinguishes it from immunosuppression.

10.3 The discovery on which the present invention is based is the fact that administration of a non-depleting anti-CD4 antibody, optionally together with a non-depleting anti-CD8 antibody, can lead to the induction of tolerance to an antigen or, in other words, induces an immunological tolerance permissive environment. In order to induce tolerance to a specific antigen it is clear that the antigen in question must be present and presented to the immune system whilst the immunological tolerance permissive environment obtains. The antigen may be present already or may need to be administered but, for example, in the case of an autoimmune condition the antigen will already be present. In addition, the identity of the antigen may or may not be clearly defined. On the one hand, where it is necessary to administer the antigen, then its identity must be known at least to some extent for it to be administered. On the other hand, in the case of an autoimmune condition, the identity of the antigen against which the immune system is reacting may not be known with any precision. However, I cannot see why this should give rise to any difficulty, or more particularly any lack of clarity in the claim, since it is clear that in this case the antigen (whatever it is) must be present.

11. DECLARATION

11.1 I further declare that all statements made herein to my knowledge are true and that all

statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

J. Scott Crowe

Date: 7th July 1995

JSC 1

Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES

Company	Product	Generic Name	Status	Comments
Johnson & Johnson	Orthoclone	OKT-3	since 1986	for transplants; for haematalogical malignancy
Xoma	XomaZyme-H65		PLA pending orphan status	for host graft disease
			Phase II	for T-cell lymphoma
Xoma	XomaZyme-Mel		Phase II	for melanoma
Xoma	XomaZyme-791		Phase I	immunotoxin for colon cancer
			preclinical	for ovarian cancer
Xoma	XomaZyme-CD 7 Plus		Phase I	for T cell malignancies
Xoma / Green Cross	TheraMabs		preclinical	hybrid antibodies
Xoma / Sterling Winthrop	ING-1		preclinical	pancarcinoma MAb
Xoma		regressens	preclinical	antigens; for breast, prostate, kidney and thyroid cancer
IDEC / Boehringerlngelheim / Zanyaku Kogyo	Specifid		Phase III	panel of anti-idiotype MAbs for B-cell lymphomas
IDEC/Lilly (Hybritech)			Phase II	yttrium-conjugated antibodies, IDEC to retain full rights
IDEC	Mel-1		Phase II	anti-idiotype for melanoma
IDEC	Mel-2		Phase I	for melanoma
ImmunoGen / Roussel-Uclaf	Oncolysin B		Phase II orphan drug	blocked-ricin conjugate, for leukemia and lymphoma
ImmunoGen	Oncolysin M		Phase II	blocked-ricin conjugate for leukemia
ImmunoGen	Oncolysin S		Phase II	MAb-toxin, anti-N901 blocked-ricin conjugate for lung cancer; licensed to Merck
ImmunoGen / Upjohn	CC-1065		preclinical	conjugate for melanoma and lymphoma
ImmunoGen	IMG-BR-C		preclinical	MAb-toxin conjugate: for breast cancer
immunoGen	IMG-BL-C		preclinical	MAb-toxin conjugate: for bladder cancer
ImmunoGen	IMG-CR		preclinical	MAb-toxin conjugate: for colorectal cancer
ImmunoGen	IMG-M		preclinical	MAb-toxin conjugate: for melanoma cancer

Continued on next page

Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES [CONT.]

Company	Product	Generic Name	Status	Comments
ImmunoGen	IMG-O		preclinical	MAb-toxin conjugate; for ovarian ca
ImmunoGen	ImmunoG		preclinical	maitansine conjugate; previously developed by Takeda
ImmunoGen	KT-NK-DI		preclinical	bifunctional antibody complex
Cytogen/ Sterling-Winthrop	Onco-Rad OV103		Phase II	antibody-yttrium-90 conjugate for ovarian cancer
Cytogen	Onco-Rad GI103		Phase I	for gastrointestinal cancer
Cytogen	Onco-Rad PR358		Phase I	for prostate cancer
Cytogen	Onco-Rad BL372		preclinical	for bladder cancer
Cytogen/Lilly			Phase I	MAbs and vinca alkaloids
Cytogen			Phase I	to remove bone marrow tumor cells
Cytogen/Matthey		Mab-technetium-99m	preclinical	radioactive
Centocor/Ajinomoto	Panorex		Phase II	murine IgG2a antibody; for pancreatic cancer
Centocor			Phase I	radiolabeled antibodies for ovarian
Centocor	ICMs		preclinical	Immune Combination Molecules chimeric antibodies for colon and pancreatic cancer
Genentech	HER-2		Phase II	chimaeric for breast and ovarian cance
Genentech/NeoRx			development	HER-2 plus radiotherapy and trichothecene
Genentech			preclinical	humanized version of HER-2
Genentech	LY-6		preclinical	
Immunomedics	ImmuRAIT-AFP-I-131		Phase II	radioimmunotherapeutics linked to MAbs; for liver and other cancers
Immunomedics	ImmuRAIT-CEA-I-131		Phase II	radioimmunotherapeutics linked to MAbs; for colorectal cancer
Immunomedics	ImmuRAIT-LL2-I-131		Phase II	for B cell lymphomas
Immunomedics	ImmuRAIT-rhenium-188		Phase I	radioisotope antibody conjugate for colorectal cancer
Immunomedics	ImmuChem		clinicals	MAb therapy
Immunomedics	ImmuRAIT-HCG-I-131		preclinical	for trophoblastic and germ cell cancers
Immunomedics	NP-4		preclinical	

Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES (CONT.)

Company	Product	Generic Name	Status	Comments
Immunomedics			preclinical	boron conjugates; for therapy and diagnosis
Lilly	KS1/4-DAVLB		Phase II	MAb-vinblastine conjugate; for lung, breast, ovarian, prostate, pancreatic and colorectal cancers
Lilly	KS1/4-MTX		Phase I	MAb-methotrexate conjugate
Lilly		antibombesin antibody	Phase I	GRP analogue; for lung cancer
Lilly		anti-EGF	Phase I	antiepidermal growth factor MAbs for lung cancer
Lilly	HYB-241		preclinical	for multidrug resistance
Lilly	28-19-8		preclinical	bispecific monoclonal antibody
Lilly (Hybritech)	LS2D617		preclinical	MAb for lung cancer
Lilly (Hybritech)	LY-191026		preclinical	cephalosporin and vinca alkaloid and enzyme antibody conjugate
Lilly (Hybritech)			preclinical	novel tumor-associated antigen, reacts to LA-20207 MAb.
Bristol-Myers Squibb (Oncogen)	L-6		Phase II	murine MAb; for lung, colon, ovarian and breast cancer
Bristol-Myers Squibb (Oncogen)	Bp-39		Phase I	murine MAb
Bristol-Myers Squibb (Oncogen)	CHL-6		Phase I	human chimaeric MAb; for lung, colon ovarian and breast cancer
Bristol-Myers Squibb (Genetic Systems)			clinical trials	human MAbs, joint development with Bayer (Cutter); for lung cancer
Bristol-Myers Squibb (Oncogen)			preclinical	immunoconjugates linking MAbs and doxorubicin or other agent for melanoma, lung cancer
Sanofi	BD-95225		Phase II	immunotoxins
ICRT/Texcellon	RFb4-ricin A		Phase II	for B-cell lymphoma
E Merck/Wistar	MAb-425	anti-EGF	Phase II	MAb binds to epidermal growth factor receptor (EGF-R); for brain, bladder and breast cancer
E Merck	EMD-62000		preclinical	binds with EGF receptor for neuroectodermal cancer
Sandoz	SDZ-ABL-364		Phase II	IgG3 MAb for stomach, breast and ling cancer

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Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES (CONT.)

Company	Product	Generic Name	Status	Comments
Medarex	MDX-11		Phase II	for leukemia, lung cancer and adjuvan use
Medarex			preclinical	bispecific MAb
Medarex/Chiron			preclinical	MAb conjugated to Trigger MAb for breast and ovarian cancer
Richter	RGH-0205		Phase II	immunomodulator
Technicione	LYM-1		Phase II	for B-cell lymphoma
Technicione	TNT-1, TNT-2		Phase I	for prostate cancer
NeoRx	NR-LU-10		Phase I	rhenium-labelled for ovarian and lung cancer
NeoRx	OncoPurge		Phase I	NR-LU-10 attached to pseudomonas exotoxin, for bone marrow transplant in breast cancer patients
NeoRx	NR-CO-02		Phase I	rhenium-labelled for lung, colorectal and breast cancer
NeoRx	NR-LU-13		Phase I	rhenium-labelled for pancarinomas
NeoRx	NR-LU-10-PE		preclinical	conjugated Mab with pseudomonas endotoxin for breast cancer
NeoRx	NR-ML-05		preclinical	for melanoma
Wellcome/ BioTechnology General	CAMPATH-1H		Phase I	in Europe: for leukemia and bone marrow transplant
Cyanamid/ Air Methods	N72-3		Phase I	antibody-targeted radioisotopes for breast, colorectal and ovarian cancer
Cyanamid			preclinical	MAbs linked to methotrexate and other cancer agents
Cyanamid/Celltech			preclinical	humanized antibodies linked to calicheamicin
Genetics Institute	3F8		Phase I	with M-CSF for neuroblastoma and melanoma: therapeutic and diagnostic
Genetics Institute/ NeoRx	GNI-250		Phase I	
Seragen	DAB-389 IL-2	IL-2 fusion toxin	Phase I	for arthritis and lymphomas
Seragen	DAB-389 MSK		preclinical	fusion toxin: for melanoma
Sterling-Winthrop/ ICRT	PRIA3		Phase I	as diagnostic
Sterling-Winthrop/ Xoma	ING-1		development	for colorectal therapy
			development	chimaeric MAb

Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES [CONT.]

Company	Product	Generic Name	Status	Comments
Protein Design Labs/ Roche	Smart Anti-Tac Antibody		Phase i	for cancer, MS, lupus
Protein Design Labs	Smart M195 Antibody		preclinical	
Protein Design Labs			preclinical	Anti-Erb-2 immunotoxin
Protein Design Labs/ Sandoz	Smart Antibody S-1		preclinical	for epithelial cell cancers
NCI	COL-1		Phase i	murine MAb for colorectal cancerr
NCI	B72-3		Phase I	for breast, colon, ovarian, lung cancer
NCI			clinical	Fab fragments of antibodies for melanoma
NCI	212Bi		preclinical	for leukemia and pancreatic cancer
NCI			preclinical	pseudomonas MAbs
Akzo			Phase i	tumor-associated antigens for colorectal, ovarian and pancreatic cancer
Akzo			Phase i	MAbs for radioimmune therapy
Green Cross	KM10-doxorubicin		preclinical	for gastrointestinal cancer
Akzo (Organon)			Phase I	tumor-associated antigens
Moffitt Res Cen/VA	HMFG1		Phase I	for colorectal and ovarian cancer
Institute Med Science, Australia			Phase I	antiganglioside antibodies for melanoma
Amersham	C46		clinical	for colorectal and lung cancer
Michigan U	5G6.4		clinical	MAb for ovarian and colon cancer
Roche			development	MAbs for colon and lung cancer licensed from Summa (Adria)
RhoMed/Syngen			development	MAbs and radioisotopes for colon cancer
Air Methods	ADEPT		development	directed enzyme prodrug therapy; for bowel cancer
Becton-Dickinson		anti-ieu 3a	development	chimeric for lymphoma
Biotherapy Systems		anti-idiotype	development	for lymphoma
Wistar	17-1A		development	for melanoma
ICI	D-0490		preclinical	MAb-ricin complex for colon cancer

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Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES (CONT.)

Company	Product	Generic Name	Status	Comments
Du Pont Merck			preclinical	for breast and ovarian cancer
Du Pont Merck			preclinical	bifunctional antibodies
Kabi Pharmacia			preclinical	MAbs for colon cancer
Kabi Pharmacia		protein A	preclinical	for use in the production of MAbs
Schering AG	TAb-250		preclinical	oncogene proteins and antibodies; for therapy and diagnosis
Quadra Logic			preclinical	MAb-porphyrin complex
Quadra Logic/ Genentech			preclinical	MAbs as immunomodulators
T Cell Sciences/ Astra		anti-TCAR MAbs	preclinical	t-cell receptor therapy for leukemia and autoimmune diseases
Ingen			preclinical	autoantibodies
Ingen			preclinical	catalytic antibodies
ImmunoTherapeutics	ImmTher		preclinical	
Molecular Oncology			preclinical	oncogene erbB2 MAb for breast cancer
Tanox Biosystems		migis antibodies	preclinical	for B cell lymphoma, leukemia and arthritis
Biogen			preclinical	humanized immunotoxin with angiogenin
Enzo Biochem			preclinical	technology to render antibodies radioactive just prior to use
Enzo Biochem (Genex)			preclinical	single-chain antibodies for colon cancer
Research Corp			preclinical	diphtheria toxin linked to MAbs
Biosciences Corp			preclinical	for leukemia, lung, breast, liver and genitourinary cancers
Cell Genesys/ Japan Tobacco			preclinical	gene targeting MAbs
Polycell (Quest)/ Chiron/ Lilly			preclinical	recombinant MAbs, using Quadroma technology
MECT Corp			preclinical	antiganglioside MAbs for melanoma
Scotgen/ Sloan Kettering			preclinical	humanized murine MAbs
Boehringer Mannheim			preclinical	
Italfarmaco			preclinical	type-1 ribosome-inactivating proteins conjugated to MAbs

Table 29.3
STATUS OF NEW AND EXISTING MONOCLONAL ANTIBODIES [CONT.]

Company	Product	Generic Name	Status	Comments
Takeda			preclinical	human MAbs for gastrointestinal cancer: to target IL-2
Ajinomoto/Nichirei	SV2-61 gamma		preclinical	murine IgG 1 antibody
Mitsubishi Kasei/ Nihon Yakuhin			preclinical	human MAbs: for uterine cancer
Hygeia	SK-1		preclinical	human MAb
Teijin			preclinical	chimeric MAbs for leukemia
Teijin			preclinical	antibody-cytostatic conjugates
Biomira/ Sterling-Winthrop			preclinical	MAbs for carbohydrate antigens
Biomira			preclinical	MAb isotope
Antisoma	AGENT		preclinical	antibody guided enzyme novel treatment for lung, breast and bowel cancer
Schering AG (Berlex)	TAb-250		preclinical	MAb to C-erb-2 oncogene protein
BioTechnology General			preclinical	monovalent MAbs
Kyowa Hakko		illudin-S derivatives	preclinical	linked to MAbs as immunotoxins
Meiji Milk			preclinical	glycoside GD2 MAbs
Asahi Chem			preclinical	human MAbs for stomach and lung cancer
Ube			preclinical	human MAbs for hepatic cancer
Yissum			preclinical	human MAbs
Yeda/Serono	CT-1		preclinical	anticellular factor: therapeutic and diagnostic
Yoshitomi			preclinical	MAb for lung cancer
Matthey			preclinical	MAb linked to platinum macromolecule
U.S. Dept. Commerce			preclinical	for breast cancer
U Alabama	125-IPM		preclinical	immunoconjugate for radiolabeled MAbs: diagnosis and therapy
Washington U	MAb1A3		preclinical	murine MAb for colon cancer
Nottingham U	105AD7		preclinical	antiidiotype for colorectal cancer
U Heidelberg	anti-APO-1		preclinical	